

FILE 'MEDLINE, CAPLUS, BIOSIS, AGRICOLA' ENTERED AT 14:25:55 ON 15 APR
2004

L1 110704 S HETEROCYCLIC
L2 339 S P450BM-3 OR P450BM3 OR P450BM
L3 3 S L2 AND L1
L4 2 DUP REM L3 (1 DUPLICATE REMOVED)
L5 0 S P450 NEAR3 BM
L6 370 S P450 AND MEGATERIUM
L7 5 S L6 AND L1
L8 3 DUP REM L7 (2 DUPLICATES REMOVED)
L9 574 S P450 AND L1
L10 80 S L9 AND OXIDATION
L11 35 S L10 AND AROMATIC
L12 23 DUP REM L11 (12 DUPLICATES REMOVED)
L13 689 S PAH AND P450
L14 901 S PAH AND P450?
L15 1 S L14 AND P450BM-3
L16 1 S L14 AND P450BM?

L12 ANSWER 7 OF 23 MEDLINE on STN DUPLICATE 4
 AN 1998372714 MEDLINE
 DN PubMed ID: 9705755
 TI Activation of **heterocyclic aromatic** amines by rat and human liver microsomes and by purified rat and human cytochrome P450 1A2.
 AU Turesky R J; Constable A; Richoz J; Varga N; Markovic J; Martin M V; Guengerich F P
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 R35 CA44353 (NCI)
 SO Chemical research in toxicology, (1998 Aug) 11 (8) 925-36.
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 LA English
 FS Priority Journals
 EM 199809
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 AB The dietary mutagens 2-amino-3,8-dimethylimidazo[4,5-f]quinoxaline (MeIQx) and 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP) are activated to genotoxins by rat and human liver cytochrome P450 (P450) 1A1- and 1A2-mediated N-oxidation. Immunquantitation of 51 human liver samples revealed a wide range in P450 1A2 expression (10-250 pmol/mg of microsomal protein, median 71 pmol/mg), with 39% of the livers containing >100 pmol/mg of protein. There was no evidence for expression of P450 1A1 (<1 pmol/mg of protein). P450 1A2 levels were correlated to MeIQx and PhIP N-oxidation rates (r = 0.83, 0.73, respectively). In male Fischer-344 and Sprague-Dawley rats, hepatic P450 1A2 ranged from 5 to 35 pmol/mg of protein, while P450 1A1 was <1 pmol/mg. Animal pretreatment with 3-methylcholanthrene, beta-naphthoflavone, or polychlorinated biphenyls (PCB) resulted inasmuch as 340-fold and >1000-fold induction of P450 1A2 and 1A1, respectively, and a 220-fold increase in N-oxidation activity. Approximately 20% of the human samples were as active in N-oxidation and conversion of MeIQx to bacterial mutagens as microsomes of PCB-pretreated rats [3-4 nmol of NHOH-MeIQx formed min-1 (mg of protein)-1]. In contrast, microsomes from PCB-treated rats displayed higher rates of PhIP N-oxidation and activation to mutagens than the most active human liver microsomes [8-24 vs 2-4 nmol of HNOH-PhIP formed min-1 (mg of protein)-1]. Recombinant human P450 1A2 showed catalytic efficiencies of MeIQx and PhIP N-oxidation that were 10-19-fold higher than purified rat P450 1A2. Cytochrome P450 1A2 expression in rodent and human liver tissue varies greatly and there are considerable differences between the enzymes in the two species in the activation of some **heterocyclic aromatic** amines, which must be considered when assessing human health risk.